Cyclopropamitosenes, Novel Bioreductive Anticancer Agents. Synthesis, Electrochemistry, and Biological Activity of 7-Substituted Cyclopropamitosenes and Related Indolequinones

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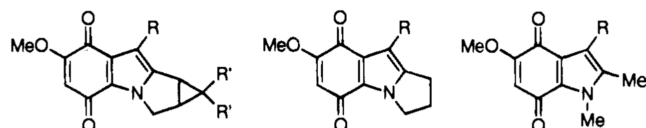
The synthesis of the indolequinones **8** and **9** starting from methyl 4-(benzyloxy)-5-methoxyindole-2-carboxylate (**10**) is described. The methoxy group in the indolequinones **1**, **2**, **4**, **5**, and **7**–**9** can be displaced by various nitrogen nucleophiles (ammonia, 2-methoxyethylamine, aziridine, 2-methylaziridine, pyrrolidine) in 22–88% yield. The resulting amino-substituted quinones, together with their methoxy precursors, were studied by cyclic voltammetry to determine their reduction potentials, which, in DMF solution, lie in the range −1.355 to −1.597 V (vs ferrocene). The cytotoxicity of the compounds towards aerobic and hypoxic mammalian cells was also determined; in general, under aerobic conditions, the cyclopropamitosenes are more toxic than the corresponding pyrrolo[1,2-*a*]indolequinones, which are in turn more toxic than the simple 1,2-dimethylindolequinones, with many of the compounds in each series showing greater toxicity toward hypoxic cells.

Introduction

We have recently described the synthesis of the 7-methoxycyclopropamitosenes **1**–**4**, together with the related indolequinones **5**–**7**.[1] The cyclopropamitosenes **1**–**4** are novel analogues of naturally occurring mitomycin antitumor agents such as mitomycin C (MMC), designed to function as bioreductive alkylating agents as indicated in Scheme 1. Therefore it was of interest to compare their properties (chemical, electrochemical, and biological) with those of the simpler indolequinones **5**–**9** as well as the archetypical bioreductive anticancer agent MMC. In this paper, we report the synthesis of the simple indolequinones **8** and **9**, together with the results of our studies on the replacement of the C-7 methoxy group with nitrogen nucleophiles to give the derivatives **19**–**37**.



1: R = CH_2OCONH_2, R′ = H
2: R = CH_2OCONH_2, R′ = Me
3: R = CH_2OCOCH_3, R′ = H
4: R = R′ = H

5: R = CH_2OCONH_2
6: R = CH_2OCOCH_3
7: R = H

8: R = CH_2OCONH_2
9: R = H

In a preliminary study of the biological properties of the cyclopropamitosenes **1** and **22**, it was shown that cytotoxic potency varied by 1000-fold.[2] The highly toxic 7-aziridinyl compound **22** was dependent upon cellular DT-diaphorase for activity, whereas this was not the case for the 7-methoxy compound **1**. In contrast, **1** showed substantially increased toxicity under anaerobic conditions, while the toxicity of **22** was unaffected. Hypoxic cells can account for a significant proportion of viable cells in solid tumors, and hence they constitute an important target for development of novel drugs.[3] Therefore, one of the purposes of this work was to establish structure/activity relationships for increased toxicity under hypoxic conditions. Previous work has shown dependence of hypoxic toxicity on redox potential for bioreductively activated nitro compounds.[4] There is also evidence to show that toxicity of mitosenes can be redox related.[5] Thus, we report here values of E_{redox} for key compounds in order to establish any role of redox potential for determining toxicity under hypoxic or aerobic conditions.

Results and Discussion

Chemistry. In order to compare the cyclopropamitosenes **1**–**4** and their "descyclopropane" analogues, **5**–**7**, with simpler derivatives, a series of indolequinones based on the simple dimethylated indole system **8** was prepared from the indole 2-ester **10** as shown in Scheme 2. The indole 2-ester **10** is a key intermediate not only in the synthesis of cyclopropamitosenes[1] but also in our synthesis of the thiazole indolequinone BE 10988, a reported inhibitor of topoisomerase II.[6] *N*-Methylation (80%) and lithium aluminum hydride reduction of the ester **10** (83%) gave the indole-2-methanol **12**, which was deoxygenated *via* its xanthate ester to give the 1,2-dimethylindole **14a**. Introduction of the formyl group by Vilsmeier reaction, debenzylation, oxidation, and elaboration of the side chain proceeded under the usual conditions[1] to give the desired indolequinone **8** (Scheme 2). The quinone **9**, lacking the side chain, was also prepared from **14a** by hydrogenolysis to give **14b** followed by Fremy's salt oxidation (Scheme 3).

The most important nonhydrolytic reaction of natural mitomycins has been the replacement of the 7-methoxy group of mitomycin A with other substituents by reac-

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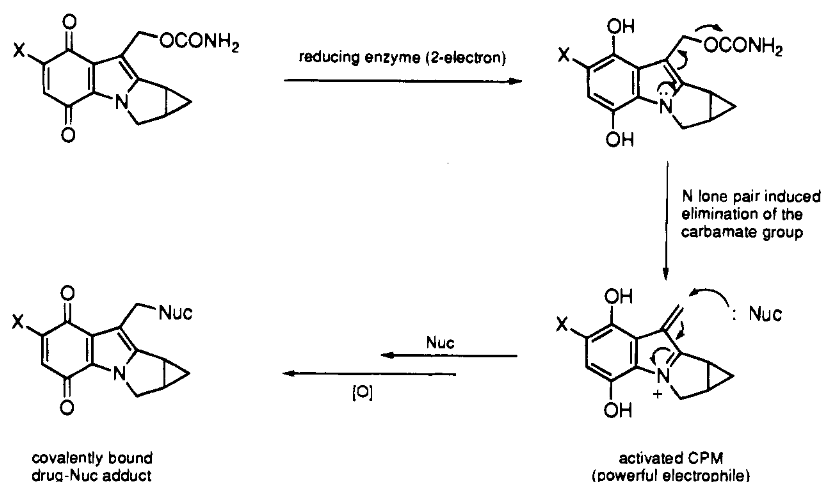
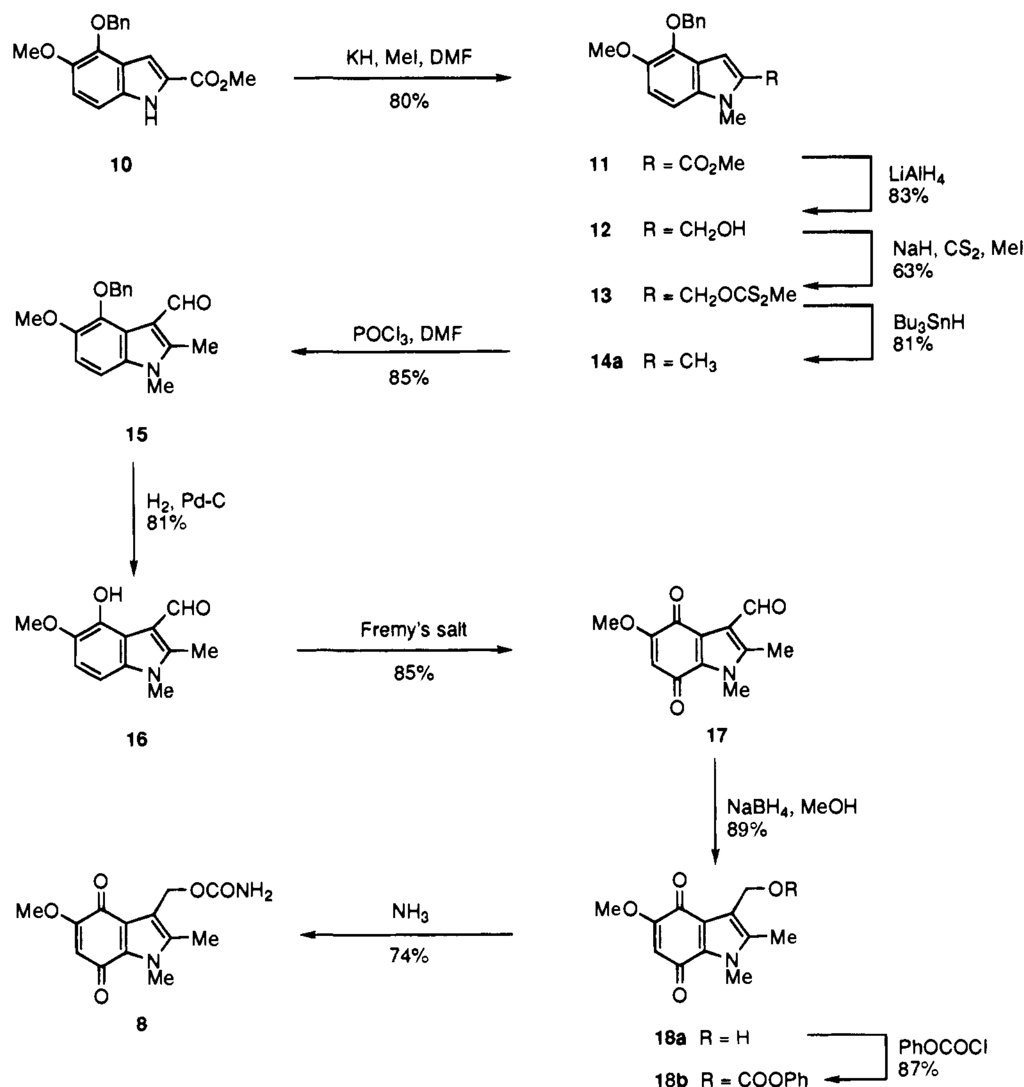
Scheme 1[a]



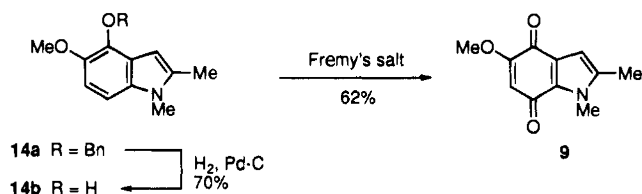
[a] For simplicity, only the 2-electron reductive activation pathway is shown; for discussion of the alternative 1-electron process, see ref 1.

Scheme 2



tion with nucleophiles such as alkoxides and amines.[7,8] Furthermore, introduction of amine groups at C-7 is claimed to modify the antitumor activity of the mitomycins and the derived mitosenes, and therefore we decided to study the displacement of the methoxy group from the cyclopropamitosenes **1**–**4** and the related indolequinones **5**–**9**. Thus, following the method of Iyengar, Remers, and Bradner,[9] the 7-methoxycyclopropamitosenes **1**, **2**, and **4** were treated with an excess of a variety of amines to give the 7-substituted cyclopropamitosenes **19**–**27** in good yield (Table **1**). The reactions could easily be followed by TLC, the orange-red methoxy compounds being converted into the purple (except the aziridinyl) amino-substituted quinones. The

Scheme 3



aziridinyl quinones, which were prepared because it is claimed that such substituents improve the anticancer activity of related mitosenes,[9,10] were red in color, presumably reflecting the reluctance of the aziridine nitrogen lone pair to delocalize into the quinone system. (**CAUTION**: all aziridines should be treated as highly toxic and handled accordingly.)

In a similar manner, the indolequinones **5** and **7** which lack the cyclopropane ring, together with the simpler 1,2-dimethylindolequinones **8** and **9**, were also converted into a variety of amine derivatives, **28**–**37** (Table 1).

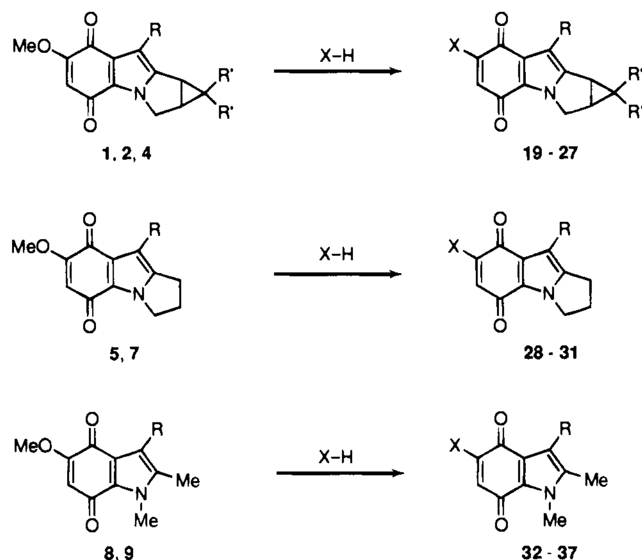


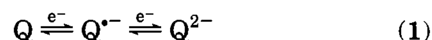
Table 1. Substitution Reactions of the Methoxyindolequinones

substrate	R	R′	X	product	yield (%)
1[a]	CH_2OCONH_2	H	NH_2	19	22[a]
1	CH_2OCONH_2	H	$MeOCH_2CH_2NH$	20	64
1	CH_2OCONH_2	H	pyrrolidinyl	21	73
1	CH_2OCONH_2	H	aziridinyl	22	76
2	CH_2OCONH_2	H	2-methylaziridinyl	23	68
2	CH_2OCONH_2	Me	pyrrolidinyl	24	73
2	CH_2OCONH_2	Me	aziridinyl	25	75
4	H	H	aziridinyl	26	84
4	H	H	2-methylaziridinyl	27	79
5	CH_2OCONH_2	–	aziridinyl	28	68
5	CH_2OCONH_2	–	2-methylaziridinyl	29	58
7	H	–	aziridinyl	30	73
7	H	–	2-methylaziridinyl	31	82
8	CH_2OCONH_2	–	pyrrolidinyl	32	71
8	CH_2OCONH_2	–	aziridinyl	33	81
8	CH_2OCONH_2	–	2-methylaziridinyl	34	88
9	H	–	pyrrolidinyl	35	84
9	H	–	aziridinyl	36	67
9	H	–	2-methylaziridinyl	37	70

[a] The substrate was the phenyl carbonate precursor to the carbamate; yield is for introduction of both NH_2 groups.

Electrochemistry. The biological mechanism of action of the mitomycins requires that they are initially activated by reduction of the quinone, although whether the first formed active species is the semiquinone radical anion or the hydroquinone (formed by 1- or 2-electron reduction, respectively) is still a matter of debate. Although, *in vivo*, the reduction is enzyme mediated, it can be readily studied in the laboratory using electrochemical techniques, and because of its importance, it is not surprising that MMC and related mitosenes have been subjected to several electrochemical studies.[11-17] Therefore, for comparison purposes, we undertook an electrochemical study of the novel cyclopropamitosenes and related indolequinones.

The electrochemical properties of various bioreductive alkylating quinones have been studied mostly using the half-wave potential ($E_{1/2}$) of the quinone reduction step.[14,15,17] We firstly determined the E_{redox} values for the **1**-electron reduction of the quinone in a nonaqueous solvent, DMF, using tetra-*n*-butylammonium tetrafluoroborate as supporting electrolyte. In dipolar aprotic solvents such as DMF, simple quinones are reduced in two successive steps which are electrochemically reversible under usual voltammetric conditions (eq **1**).[18]



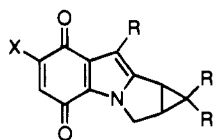
$$Q \overset{e^-}{\rightleftharpoons} Q^{\bullet -} \overset{e^-}{\rightleftharpoons} Q^{2-} \quad (1)$$

However, from previous studies on MMC,[12] it has been shown that although the first step in the redox process is reversible, or at least quasi-reversible, in DMF, the second step (which occurs at a more negative potential) is essentially irreversible, in contrast to simple quinones. Hence we concentrated on the first step in the process.

Cyclic voltammograms at various scan rates showed that the **1**-electron reduction of the cyclopropamitosenes is at least quasi-reversible in DMF. The E_{redox} values, tabulated with reference to ferrocene (Fc) to avoid liquid junction potential, are shown in Tables 2–4. Several trends are apparent: for the cyclopropamitosenes (Table 2): the aziridinyl derivatives are easiest to reduce, but the methoxy compound **1** is still more easily reduced than MMC, which under our conditions has an E_{redox} of −**1**.421 V(Fc), equivalent to −0.88 V(ssce) (lit.[12] −0.92 V). The aziridine ring, because of its inability to donate electron density into the quinone which would involve an unfavorable "flattening" of the aziridine nitrogen, has a similar electronic effect to the methoxy group as reflected in their σ_p values (aziridine = −0.25,[16] methoxy = −0.28[19]), whereas the other amine substituents are much more electron releasing (*e.g.*, pyrrolidinyl, σ_p = −0.77[16]), and therefore these quinones (*e.g.*, **21** and **24**) are more difficult to reduce. The differences in the redox potential between the various derivatives are relatively small, although it is clear that compounds possessing the C-10 side chain are easier to reduce than those without it. However, the cyclopropane ring itself does have some effect, in that, for example, the cyclopropamitosenes **22**, **23**, **26**, and **4** are all easier to reduce than the equivalent pyrroloindolequinones **28**–**30** and **7** which lack the cyclopropane ring. Interestingly, the simpler dimethylindolequinones with equivalent substituents (**33**, **34**, **36**, and **9**) are easier to reduce than the pyrroloindolequinones. Presumably the substituents at the 1- and 2-positions (indole numbering) incorporating ring fusion affect the overall properties of the quinone π-system.

Some electrochemical experiments were also carried out in aqueous solution using a mixture of DMF and pH 7.4 phosphate buffer. In water, of course, the

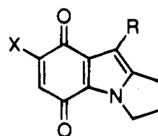
Table 2. Reduction Potentials (DMF), Biological Activity, and log *P* Values of Cyclopropamitosenes[a]



	R	R′	X	E_{redox} (V) vs Fc	log *P*	IC_{50} (air) (μmol dm^{-3})	IC_{50} (N_2) (μmol dm^{-3})	ratio
22	CH_2OCONH_2	H	aziridinyl	−1.360	1.05	0.003	0.003	1[b]
23	CH_2OCONH_2	H	2-methylaziridinyl	−1.371	1.19	1.2	0.06	20
1	CH_2OCONH_2	H	MeO	−1.395	0.65	4.8	0.14	34[b]
2	CH_2OCONH_2	Me	MeO	−1.370		3.0	0.12	25
3	CH_2OCOCH_3	H	MeO	−1.380		12	1.2	10
19	CH_2OCONH_2	H	NH_2			110	10	11
20	CH_2OCONH_2	H	$MeOCH_2CH_2NH$	−1.552		500	250	2
21	CH_2OCONH_2	H	pyrrolidinyl	−1.572		140	140	1
24	CH_2OCONH_2	Me	pyrrolidinyl	−1.588				
25	CH_2OCONH_2	Me	aziridinyl	−1.355				
MMC	–	–	–	−1.421		0.8	0.4	2
26	H	H	aziridinyl	−1.384	1.47	7	2	3.5
27	H	H	2-methylaziridinyl	−1.401	1.48	90	3.5	25
4	H	H	MeO	−1.403	1.71	200	200	1

[a] E_{redox} (±0.010 V) calculated as $(E_{pc} + E_{pa})/2$ from 100 mV s^{-1} cyclic voltammograms. E_{pc} = cathodic peak potential. E_{pa} = anodic peak potential. [b] Reference 2.

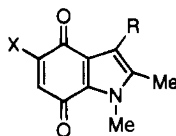
Table 3. Reduction Potentials (DMF) and Biological Activity of Pyrrolo[1,2-*a*]indolequinones[a]



	R	X	E_{redox} (V) vs Fc	IC_{50} (air) (μmol dm^{-3})	IC_{50} (N_2) (μmol dm^{-3})	ratio
28	CH_2OCONH_2	aziridinyl	−1.385	0.07	0.005	14
29	CH_2OCONH_2	2-methylaziridinyl	−1.395	0.2	0.07	3.5
5	CH_2OCONH_2	MeO		6	0.1	60
6	CH_2OCOCH_3	MeO	−1.387	11	0.45	24
30	H	aziridinyl	−1.398	2.2	1.1	2
31	H	2-methylaziridinyl		80	4	20
7	H	MeO	−1.412	300	300	1

[a] E_{redox} (±0.010 V) calculated as $(E_{pc} + E_{pa})/2$ from 100 mV s^{-1} cyclic voltammograms. E_{pc} = cathodic peak potential. E_{pa} = anodic peak potential.

Table 4. Reduction Potentials (DMF) and Biological Activity of 1,2-Dimethylindolequinones[a]



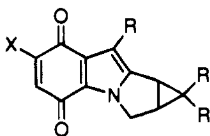
	R	X	E_{redox} (V) vs Fc	IC_{50} (air) (μmol dm^{-3})	IC_{50} (N_2) (μmol dm^{-3})	ratio
33	CH_2OCONH_2	aziridinyl	−1.368	0.5	0.025	20
34	CH_2OCONH_2	2-methylaziridinyl	−1.384	4	0.7	6
8	CH_2OCONH_2	MeO	−1.387	25	0.3	83
32	CH_2OCONH_2	pyrrolidinyl	−1.597	1000	1000	1
36	H	aziridinyl	−1.392	100	25	4
37	H	2-methylaziridinyl	−1.399	75	4	19
9	H	MeO	−1.393	270	180	1.5
35	H	pyrrolidinyl	−1.597	550	550	1

[a] E_{redox} (±0.010 V) calculated as $(E_{pc} + E_{pa})/2$ from 100 mV s^{-1} cyclic voltammograms. E_{pc} = cathodic peak potential. E_{pa} = anodic peak potential.

electrochemical reduction of quinones assumes even greater complexity in that all protonated forms of the various intermediates are possible. Cyclic voltammograms for the cyclopropamitosenes **1** and **4** indicated that quinone **4** exhibits reversibility whereas that of **1** is complex, presumably as a result of irreversible chemical change associated with the expulsion of the leaving group at C-10 upon reduction. This latter property is obviously an important factor in the ability of the compound to act as an alkylating agent. The results for indolequinones **1**, **4**, **24**, and **27** are summarized in Table 5; the corresponding values for MMC and 1,4-benzoquinone under our conditions are also shown.

Although the data set is much smaller, the same overall trends for reduction in aqueous solution hold as in the DMF experiments. Thus, indolequinones lacking the C-10 substituent are more difficult to reduce, and replacement of the methoxy group with a secondary

Table 5. Reduction Potentials of Cyclopropamitosenes in Aqueous Solution[a]



compound	R	R′	X	E_{pc} (V) vs ssce	$E_{pc} - E_{p/2}$ (mV)	i_{pa}/i_{pc}
1	CH_2OCONH_2	H	MeO	−0.425	25	0.52
4	H	H	MeO	−0.455	55	1.04
24	CH_2OCONH_2	Me	pyrrolidinyl	−0.525	45	0.44
27	H	H	2-methylaziridinyl	−0.420	55	1.09
MMC	–	–	–	−0.455	45	0.87
benzoquinone	–	–	–	−0.010	50	0.98

[a] $E_{p/2}$ = half-cathodic peak potential determined at 100 mV s^{-1}. $E_{p/2} = E_{1/2} + 28/n$ mV at 25 °C (where n = number of electrons). $E_{1/2}$ = half-wave potential. i_{pa} = anodic peak current. i_{pc} = cathodic peak current.

amine other than aziridines causes the expected increase in reduction potential.

Additional information can also be obtained from Table 5. The value of $E_{pc} - E_{p/2}$ (56.2/n mV) indicates the number of electrons transferred in the process; thus the implication is that the 7-methoxycyclopropamitosene **1** undergoes a 2-electron reduction to the hydroquinone, complicated by irreversibility as a result of chemical steps, whereas the quinones **4** and **27** are simply reduced (reversibly) to the semiquinone radical anion.

Biological Studies. Reductive activation of the novel cyclopropamitosenes and related indolequinones that will lead to toxicity toward cells in culture can occur in two ways. Firstly, by *initial* 1-electron reduction (by enzymes such as cytochrome P450 reductase) to give a semiquinone radical anion, in a process that is potentially reversible by oxygen,[13] *i.e.*, O_2 will inhibit toxicity. Secondly, by an initial 2-electron reduction to give a hydroquinone, in a process generally carried out by the obligate 2-electron reductase DT-diaphorase in a process that is O_2-independent. The subsequent level of the ultimate alkylating species will then be governed by any disproportionation reaction between the semi- and hydroquinones.[20-22] In order to investigate the effect of oxygen on the cytotoxicity of cyclopropamitosenes, experiments were performed under air and under nitrogen. Thus, Chinese hamster V79 cells were exposed to the cyclopropamitosenes and related indolequinones for 3 h at 37 °C under aerobic or anaerobic (N_2) conditions. Toxicity was measured using the MTT assay,[23] and typical survival curves are given in Figure 1. From data such as these, values of IC_{50}, the concentration required to kill 50% of the cells, are determined. In the example in Figure 1 where V79 cells are exposed to compounds **8** and **33** in air (open symbols), values of IC_{50} are 25 and 0.5 μmol dm^{-3}. Both **8** and **33** show substantially greater toxicity under hypoxic conditions (filled symbols), giving IC_{50} values of 0.3 and 0.025 μmol dm^{-3} which correspond to an 80- and 20-fold increase in toxicity, respectively. Values of IC_{50} for all the compounds studied are recorded in Tables 2–4.

Lipophilicity values (log P) are also recorded for some cyclopropamitosenes in Table 2. The compounds containing the carbamate moiety in the 9-position show greater hydrophilic character than the corresponding unsubstituted indolequinones. Maliepaard *et al.* demonstrated a strong correlation between log P and cytotoxic activity of a range of related mitosenes, with potency increasing with log P up to about a value of 3.0.[14] However, no such trend is apparent with the compounds examined in the present work.

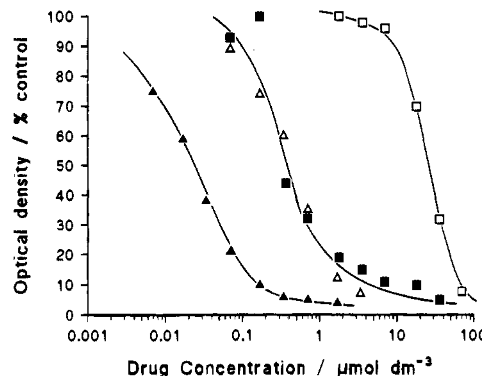


Figure 1. MTT assay of V79 cells following treatment with **8** (□, ■) or **33** (Δ, ▲) under aerobic (open symbols) or hypoxic (filled symbols) conditions. Change in optical density as a function of concentration of mitosene. Cells exposed to test compound for 3 h at 37 °C. Points are mean values derived from up to six independent experiments. Curves were fitted by eye.

The activities of the indolequinones span a large range, with the 7-aziridinylcyclopropamitosene **22** being the most active (nanomolar range). In terms of structure/activity relationships, our main interest was the effect of the cyclopropane ring, and the IC_{50} values for 11 cyclopropamitosenes are recorded in Table 2. Only the aziridine **22** is more active than MMC in air; presumably the aziridine and carbamate both act as electrophilic sites. To date there is no evidence to suggest that the compound is trifunctional (with involvement of the cyclopropane) as has been suggested for the related aziridinylindolequinone EO9, which has an IC_{50} of around 0.1 μmol dm^{-3} in air.[2,24-26] Alternatively the higher potency of **22** over MMC in air may be due to the fact that it is activated by DT-diaphorase in V79 cells, and MMC less so.[2] However under anaerobic conditions, the 7-(2-methylaziridinyl) compound **23** and the 7-methoxycyclopropamitosenes **1** and **2** all become more toxic than MMC. This possibly means that they are better substrates for 1-electron reductases than MMC or reflects the differences in the stability of the semiquinone radical anion (and hence the position of equilibrium between semiquinone and hydroquinone). It is also noteworthy that the 7-aminocyclopropamitosene **19** is considerably less potent than MMC.

The cyclopropane ring does appear to have some effect, since, in general, under aerobic conditions, the cyclopropamitosenes are more toxic than the corresponding pyrrolo[1,2-*a*]indolequinones, which are in turn more

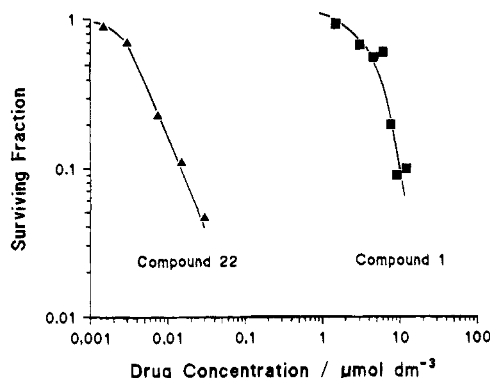


Figure 2. Clonogenic assay: surviving fraction as a function of drug concentration for cells exposed to 1 or **22** for 3 h at 37 °C in air. Points are mean values derived from up to five independent experiments. Curves were fitted by eye.

toxic than the simple 1,2-dimethylindolequinones. Within each series of compounds (except the least potent simple 1,2-dimethylindolequinones), the aziridinyl compounds are more active than the corresponding 2-methylaziridines, which are more active than the methoxy compounds. The most extreme example of this is shown in Figure 2 which compares the toxicity of **22** and **1** in air. This set of data shows results of clonogenic cell survival experiments (which is a different end point from the MTT assay). The difference in cytotoxic efficiency of these compounds (Figure 2) is about 1000, and this is comparable with the results recorded in Table 2 (MTT assay). A probable explanation for this large difference is that, following bioreductive activation, the aziridine in **22** (not the methoxy in **1**) will act as a potent electrophilic alkylating center. The 400-fold difference in aerobic toxicity between **22** and **23**, where the aziridine is substituted by a 2-methylaziridine, is less easily explicable. However, it is our experience, with other series of bioreductive drugs,[27,28] that methyl substitution of aziridines considerably reduces their alkylating and hence cytotoxic efficiency. Factors that may contribute to this include steric effects and/or changes in the pK_a of the aziridine nitrogen following bioreductive activation. An alternative possibility could be that the aziridine-containing indolequinones are more easily reduced under biological conditions (relative to the corresponding methylaziridine or methoxy compounds), although the electrochemical results suggest that the differences in reduction potential are relatively small. In previous work on bioreductive activation of aromatic nitro compounds, which are substrates for many of the same enzymes that can reductively metabolize quinones,[3] it was found that a 100 mV change in redox potential (to a more positive value) was required to increase potency by 10-fold.[4,29] The relationship of changing cytotoxic potency with redox potential was similar in air or under hypoxic conditions.[30] Therefore, in the present series of compounds, it is unlikely that small differences in the redox potential of the parent indolequinones will contribute significantly to the observed differences in potency in air and hypoxia. This interpretation is consistent with recent findings on related mitosenes.[15]

Many of the compounds in each series show greater toxicity toward hypoxic cells. In particular, the 7-methoxy compounds containing a carbamate in the 9-position have the highest differential toxicity (values of the ratio air:hypoxic range from 34 to 83). The presence of oxygen is likely to affect the lifetime and/or the relative proportions of the reduced quinone species (*i.e.*, the semiquinone or the hydroquinone), and it is one of these species that will expel the carbamate and act as a center for reaction with nucleophiles (Scheme 1). In contrast when the 9-position is unsubstituted, it is always compounds carrying the 7-(2-methylaziridinyl) group that show the highest values of differential toxicity, *i.e.*, under these reducing conditions, with no putative leaving group in the molecule, it is likely that the methylaziridine becomes activated to a more efficient alkylating moiety.

In summary, we have developed structure/activity relationships for two biological properties relevant to the application of mitosenes in cancer therapy. Firstly, novel mitosenes of higher potency than MMC have been prepared. Secondly, many of these agents show a much greater hypoxic/oxic differential than MMC, *i.e.*, they have high selectivity toward hypoxic cells. Such compounds that are significantly more active under hypoxic conditions offer some promise as selective treatments for hypoxic tumor cells and therefore may be useful in the treatment of cancer when directed toward this tumor cell population which is potentially resistant to radio- and chemotherapy. Further chemical and biological studies are in progress, aimed at firstly delineating some of the mechanistic features of these novel cyclopropamitosenes, in particular their substrate specificity for the enzymes known to be important in bioreductive activation (DT-diaphorase, cytochrome P450 reductase, *etc.*), and secondly establishing antitumor effects of **1** and **22** in rodent model systems. These results will be reported elsewhere.

Experimental Section

For general experimental details, see ref 6. All J values are given in hertz (Hz).

Methyl 4-(Benzyloxy)-5-methoxy-1-methylindole-2-carboxylate (11). To a stirred suspension of potassium hydride (0.94 g, 23 mmol) in DMF (30 mL) at 0 °C was added dropwise a solution of methyl 4-(benzyloxy)-5-methoxyindole-2-carboxylate (**10**) (4.85 g, 15.6 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 45 min. Iodomethane (2.43 g, 17.1 mmol) was added dropwise at 0 °C and the mixture allowed to warm to room temperature. The reaction was monitored by TLC and was complete within 1 h. Saturated ammonium chloride solution was added, and the mixture was extracted with ether. The ether layer was washed twice with water, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (60% petroleum ether/40% ether) to give 11 (4 g, 80%) as a colorless crystalline solid: mp 53–54 °C; IR ($CHCl_3$) 2932, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (6 H, m, Ar-H, 3-H), 7.11 and 7.01 (each 1 H, d, J = 9.0, 6,7-H), 5.25 (2 H, s, OCH_2Ph), 4.00 (3 H, s, NMe), 3.88 (6 H, s, OMe); ^{13}C NMR ($CDCl_3$) δ 162.48, 145.06, 141.67, 137.97, 136.99, 128.35, 128.15, 128.01, 127.86, 127.75, 121.32, 115.93, 107.31, 105.41, 75.03 (OCH_2Ph), 58.50, 51.60 (Me), 31.78 (NMe). Anal. ($C_{19}H_{19}NO_4$) C, H, N.

4-(Benzyloxy)-5-methoxy-1-methylindole-2-methanol (12). To a stirred suspension of lithium aluminum hydride (2.8 g, 73 mmol) in THF (50 mL) at 0 °C was added dropwise a solution of ester 11 (4 g, 12 mmol) in THF (30 mL). After the addition was complete, the mixture was stirred at room temperature for 1 h. Careful additions of water (5 mL) and silica gel (10 g) were made. The gray granular precipitate was filtered off. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure yielding **12** (4.2 g, 83%) as a colorless crystalline solid: mp 41–42 °C; IR ($CHCl_3$) 3424 (OH), 3000 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (2 H, d, J 7.5, Ar-H), 7.19 (3 H, m, Ar-H), 6.89 (2 H, d, J = 3.6, Ar-H), 6.36 (1 H, s, CH=C), 5.15 (2 H, s, CH_2Ph), 4.57 (2 H, s, CH_2OH), 3.84 (3 H,

s, NMe), 3.56 (3 H, s, OMe); ^{13}C NMR ($CDCl_3$) δ 145.09, 141.12, 139.32, 138.46, 135.72, 128.54, 128.41, 128.24, 128.13, 127.99, 122.21, 112.02, 104.65, 98.53, 75.17 (OCH_2Ph), 58.67 (OMe), 57.40 (CH_2OH), 30.08 (NMe).

Xanthate 4-(Benzyloxy)-5-methoxy-1-methylindole-2-methanol (13). A solution of alcohol **12** (2.9 g, 9.8 mmol) in THF (30 mL) was added dropwise at 0 °C to a stirred suspension of NaH (0.38 g, 15.8 mmol) in THF (40 mL). The mixture was stirred at room temperature for 1 h and then refluxed for 1 h. Carbon disulfide (3.7 g, 48 mmol) was added dropwise and the mixture refluxed for 30 min. Iodomethane (6.9 g, 48 mmol) was added dropwise and the mixture refluxed for a further 30 min. A few drops of acetic acid were added, and the crude mixture was extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to a yellow solid. The crude product was purified by column chromatography (10% gradient elution: 100% petroleum ether–50% petroleum ether/50% ether) to yield **13** (2.38 g, 63%) as a yellow crystalline solid: mp 88–89 °C; IR ($CHCl_3$) 3064, 2932, 1632, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (2 H, m, Ar-H), 7.49 (3 H, m, Ar-H), 6.94 (2 H, m, Ar-H), 6.47 (1 H, s, CH=C), 5.20 (2 H, s, OCH_2Ph), 4.41 (2 H, s, CH_2OS_2-Me), 3.86 (3 H, s, NMe), 3.60 (3 H, s, SMe); ^{13}C NMR ($CDCl_3$) δ 188.89 (C=S), 145.17, 140.78, 138.24, 135.26, 133.96, 128.30, 128.00, 127.73, 122.27, 111.94, 104.35, 99.83, 74.93 (OCH_2-Ph), 58.46 (OMe), 29.69 (NMe), 26.56 (CH_2OCS_2Me), 13.17 (SMe). Anal. ($C_{20}H_{21}NO_3S_2$) C, H, N.

4-(Benzyloxy)-5-methoxy-1,2-dimethylindole (14a). To a solution of the xanthate **13** (1.7 g, 4.4 mmol) in benzene (15 mL) was added tributyltin hydride (2.0 g, 6.9 mmol) and AIBN (0.04 g, 0.3 mmol). The mixture was refluxed for 5 h. The mixture was concentrated and the crude product purified by column chromatography (10% gradient: 100% petroleum ether–30% petroleum ether/70% ether) yielding **14a** (1.0 g, 81%) as a colorless crystalline solid, mp 47–48 °C; IR ($CHCl_3$) 2938, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (2 H, m, Ar-H), 7.41 (3 H, m, Ar-H), 6.27 (1 H, s, CH=C), 5.20 (2 H, s, OCH_2Ph), 3.87 (3 H, s, NMe), 3.56 (3 H, s, OMe), 2.36 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 144.99, 140.34, 138.48, 137.10, 134.81, 128.27, 127.95, 127.63, 122.52, 110.14, 103.92, 96.68, 74.83 (OCH_2-Ph), 58.44 (OMe), 29.54 (NMe), 12.83 (Me). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

4-(Benzyloxy)-5-methoxy-1,2-dimethylindole-3-carboxaldehyde (15). DMF (0.95 g, 13 mmol) and phosphorus oxychloride (0.44 g, 2.8 mmol) were stirred at −5 °C for 30 min. A solution of indole **14a** (0.74 g, 2.6 mmol) in DMF (3 mL) was added slowly dropwise, maintaining the temperature below 10 °C. After the addition was complete, the mixture was stirred at 35 °C for 1 h. Ice water (5 mL) followed by sodium hydroxide solution (37%, 5 mL) was added and the mixture extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated. The crude solid was recrystallized (dichloromethane/petroleum ether) yielding **15** (0.68 g, 85%) as colorless crystals: mp 131–132 °C; IR ($CHCl_3$) 2996, 2936, 1638, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.52 (1 H, s, CHO), 7.48 (2 H, m, Ar-H), 7.34 (3 H, m, Ar-H), 6.98 (2 H, m, Ar-H), 5.17 (2 H, s, OCH_2Ph), 3.93 (3 H, s, NMe), 3.64 (3 H, s, OMe), 2.77 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 188.10 (CHO), 147.88, 145.31, 141.03, 137.47, 133.46, 128.44, 128.04, 121.81, 113.70, 110.38, 105.09, 74.77 (OCH_2Ph), 57.60 (OMe), 29.49 (NMe), 12.40 (Me). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

4-Hydroxy-5-methoxy-1,2-dimethylindole-3-carboxaldehyde (16). Indole-3-carboxaldehyde **15** (0.68 g, 2.2 mmol) was dissolved in THF (30 mL). A catalytic quantity of 10% palladium/carbon was added. The reaction mixture was shaken under a hydrogen pressure of 45 psi for 12 h. The catalyst was removed by filtering the crude mixture through Celite. Concentration under reduced pressure followed by column chromatography (EtOAc) yielded **16** (0.39 g, 81%) as a yellow solid: mp 173–174 °C; IR ($CHCl_3$) 3180, 2940, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.14 (1 H, br s, OH), 9.44 (1 H, s, CHO), 6.90 (1 H, d, J = 8.6, Ar-H), 6.59 (1 H, d, J = 8.6, Ar-H), 3.91 (3 H, s, NMe), 3.57 (3 H, s, OMe), 2.52 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 183.62 (CHO), 150.11, 142.92, 141.16, 134.14, 115.28, 115.18, 112.27, 99.63, 57.67 (OMe), 30.04 (NMe), 10.67 (Me); HRMS found (M^+) 219.0895, $C_{12}H_{13}NO_3$ requires (M) 219.0895.

3-Formyl-5-methoxy-1,2-dimethylindole-4,7-dione (17). A solution of potassium nitrosodisulfonate (1.32 g, 4.9 mmol) in water (48 mL) was added to a stirred solution of indole **16** (0.36 g, 1.6 mmol) in acetone (25 mL) buffered with aqueous sodium dihydrogen phosphate (0.17 M, 31 mL). The mixture was stirred for 2 h and monitored by TLC. The mixture was concentrated and the resulting residual oil extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography (EtOAc) to yield **17** (0.32 g, 85%) as an orange solid: mp 246–247 °C; UV (MeOH) 219 (log ε 4.30), 244 (4.07), 292 (4.18), 328 (3.68), 439 nm (3.13); IR ($CHCl_3$) 3020, 1678, 1638, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.53 (1 H, s, CHO), 5.70 (1 H, s, 6-H), 3.93 (3 H, s, NMe), 3.85 (3 H, s, OMe), 2.61 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 187.99 (CHO), 178.94, 177.60 (C=O), 159.68, 142.62, 128.99, 122.80, 119.80, 106.61, 55.66 (OMe), 32.13 (NMe), 11.21 (Me). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

3-(Hydroxymethyl)-5-methoxy-1,2-dimethylindole-4,7-dione (18a). Sodium borohydride (0.29 g, 7.6 mmol) was added to a stirred solution of quinone **17** (0.3 g, 1.2 mmol) in MeOH (60 mL). After 2 h, acetone (2.5 mL) was added followed by aqueous iron(III) chloride (1 M, 1.5 mL) in hydrochloric acid (0.1 M, 1.5 mL). The mixture was immediately extracted with dichloromethane. The combined extracts were washed with water and brine and dried ($MgSO_4$). The organic layer was concentrated to give **18a** (0.27 g, 89%) as an orange-red crystalline solid: mp 199–200 °C; UV (MeOH) 228 (log ε 3.74), 288 (3.74), 348 (3.00), 495 nm (2.71); IR ($CHCl_3$) 3488, 2972, 1660, 1636, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.18 (1 H, s, 6-H), 4.62 (2 H, s, CH_2OH), 3.87 (3 H, s, NMe), 3.83 (3 H, s, OMe), 2.33 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 179.16, 178.57 (C=O), 159.62, 134.70, 129.17, 122.69, 121.58, 107.07, 56.56 (OMe), 55.85 (CH_2OH), 32.35 (NMe), 9.52 (2-Me); HRMS found (M^+) 235.0845, $C_{12}H_{13}NO_4$ requires (M) 235.0844.

5-Methoxy-1,2-dimethyl-3-[[(phenoxycarbonyl)oxy]methyl]indole-4,7-dione (18b). Phenyl chloroformate (0.6 g, 3.86 mmol) was added dropwise to a stirred solution of quinone **18a** (0.23 g, 0.96 mmol) in dry pyridine (15 mL). The mixture was stirred at 0 °C for 2 h, after which water (30 mL) was added. The mixture was extracted with dichloromethane, and the combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The resulting residue was purified by column chromatography (EtOAc) to yield **18b** (0.29 g, 87%) as an orange solid: mp 144–145 °C; UV (MeOH) 228 (log ε 4.23), 288 (4.21), 345 (3.47), 453 nm (3.14); IR (film) 3020, 2940, 1675, 1670, 1652, 1641, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (5 H, m, Ph), 5.64 (1 H, s, 6-H), 5.44 (2 H, s, CH_2OCO_2-Ph), 3.91 (3 H, s, OMe), 3.82 (3 H, s, NMe), 2.33 (3 H, s, Me).

3-[(Carbamoyloxy)methyl]-5-methoxy-1,2-dimethylindole-4,7-dione (8). A solution of the phenyl carbonate **18b** (0.28 g, 0.79 mmol) in dichloromethane (40 mL) was cooled to −78 °C. Ammonia gas was bubbled into the solution for 2 h. The reaction was stirred overnight and allowed to warm to room temperature. The crude mixture was concentrated and recrystallized (acetonitrile/benzene) to give **8** (0.16 g, 74%) as orange crystals: mp 164 °C dec; UV (MeOH) 228 (log ε 4.11), 288 (4.11), 348 (3.39), 454 nm (3.07); IR (film) 3050, 2975, 1730, 1675, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$–DMSO-d) δ 5.63 (1 H, s, 6-H), 5.23 (4 H, br s, CH_2OCONH_2), 3.90 (3 H, s, OMe), 3.81 (3 H, s, NMe), 2.31 (3 H, s, Me); HRMS found (M^+) 278.0903, $C_{13}H_{14}N_2O_5$ requires (M) 278.0902.

5-Methoxy-1,2-dimethylindol-4-ol (14b). Indole **14a** (0.46 g, 1.6 mmol) was dissolved in EtOAc (12 mL). A catalytic quantity of palladium/carbon (10%) was added. The reaction was shaken under a hydrogen pressure of 45 psi for 12 h. The catalyst was removed by filtering the crude mixture through Celite. Concentration under reduced pressure yielded **14b** (0.31 g, 70%) as a colorless crystalline solid: mp 114–115 °C; IR ($CHCl_3$) 3532, 2992, 1398 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.85 (1 H, d, J = 8.7, Ar-H), 6.70 (1 H, d, J = 8.7, Ar-H), 6.30 (1 H, s, CH=C), 5.83 (1 H, br s, OH), 3.88 (3 H, s, NMe), 3.56 (3 H, s, OMe), 2.37 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 138.72, 137.66, 136.70, 134.90, 117.16, 107.87, 99.86, 96.04 (C=C), 58.32 (OMe), 29.55 (NMe), 12.84 (Me). Anal. ($C_{11}H_{13}NO_2$) C, H, N.

5-Methoxy-1,2-dimethylindole-4,7-dione (9). A solution of potassium nitrosodisulfonate (0.13 g, 0.48 mmol) in water

(5 mL) was added to a stirred solution of indole **14b** (0.03 g, 0.17 mmol) in acetone (10 mL) buffered with aqueous sodium dihydrogen phosphate (0.1 M, 5 mL). The mixture was stirred for 2 h and monitored by TLC. The mixture was concentrated and the resulting residual oil extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography (gradient elution: 70% petroleum ether/30% ether−100% ether) to yield **9** (0.02 g, 62%) as an orange solid: mp 195−196 °C; UV (MeOH) 228 (log ε 4.31), 287 (4.31), 345 (3.51), 455 nm (3.19); IR ($CHCl_3$) 1670, 1636, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (1 H, s), 5.61 (1 H, s), 3.88 (3 H, s, NMe), 3.81 (3 H, s, OMe), 2.26 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 178.76, 177.05 (C=O), 159.69, 137.94, 129.78, 124.09, 106.92, 106.67, 56.42 (OMe), 32.26 (NMe), 11.97 (Me). Anal. ($C_{11}H_{13}NO_2$) C, H, N.

7-Amino-9-[(carbamoyloxy)methyl]-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (19). 7-Methoxy-9-[[(phenoxycarbonyl)oxy]methyl]-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (0.012 g, 0.032 mmol) in concentrated ammonium hydroxide solution (5 mL) was heated at 65−70 °C until all starting material had been consumed (TLC) and the solvent removed *in vacuo*. Chromatography (Sephadex, LH-20; 50% dichloromethane/50% MeOH) of the residue gave **19** (0.002 g, 22%) as a purple crystalline solid: UV (EtOH, qualitative) 216, 245, 315, 363 (sh), 529 nm; ^1H NMR ($CDCl_3$−acetone-*d*) δ 5.36 (1 H, s, 6-H), 5.20 and 5.28 (each 1 H, d, *J* = 12.5, 10-H), 4.24 (2 H, m, 3-H), 3.40 (2 H, br s, NH_2), 2.48 (1 H, m, 1-H), 2.33 (2 H, m, 2-H), 1.29 and 0.55 (each 1 H, m, 1a-H); HRMS found (M^+) 287.0906, $C_{14}H_{13}N_3O_4$ requires (M) 287.0906.

9-[(Carbamoyloxy)methyl]-7-[(2-methoxyethyl)amino]-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (20). A solution of the carbamate 1 (0.012 g, 0.040 mmol) in dry DMF (2.5 mL) was treated with an excess of 2-methoxyethylamine (0.5 mL), and this mixture was stirred at room temperature under nitrogen for 15 h. After this time, water was added (5 mL) and the mixture extracted with dichloromethane (3 × 25 mL). The dichloromethane extracts were washed with water (4 × 25 mL) and brine (30 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a purple solid which was purified by chromatography (EtOAc) followed by recrystallization from dichloromethane/petroleum ether to give **20** (0.009 g, 64%) as a purple solid: mp 216−218 °C; UV (MeOH) 215 (log ε 4.29), 247 (4.39), 317 (4.14), 537 nm (3.13); IR ($CHCl_3$) 3544, 3424, 3368, 1722, 1662, 1610, 1588, 1288, 1262 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.20 (1 H, br s, NH), 5.27 (2 H, m, 10-H), 5.11 (1 H, s, 6-H), 4.61 (2 H, br s, NH_2), 4.27 (2 H, m, 3-H), 3.59 (2 H, t, *J* = 5.2, 2′-H), 3.38 (3 H, s, OMe), 3.28 (2 H, m, 1′-H), 2.48 (1 H, m, 1-H), 2.32 (1 H, m, 2-H), 1.30 and 0.56 (each 1 H, m, 1a-H); HRMS found (M^+) 345.1318, $C_{17}H_{19}N_3O_5$ requires (M) 345.1325.

9-[(Carbamoyloxy)methyl]-7-(pyrrolidin-1-yl)-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (21). A solution of the carbamate 1 (0.010 g, 0.033 mmol) in dry DMF (1.5 mL) was treated with pyrrolidine (0.008 mL, 0.099 mmol), and this mixture was stirred at room temperature under nitrogen for 15 h. Workup as above gave **21** (0.008 g, 73%) as a purple solid: mp 210 °C dec; UV (MeOH, qualitative) 247, 328, 549 nm; IR ($CHCl_3$) 3612, 3408, 1726, 1686, 1608, 1544, 1498, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (2 H, AB, *J* = 12.4, 10-H), 5.17 (1 H, s, 6-H), 4.55 (2 H, br s, NH_2), 4.29 (2 H, m, 3-H), 3.64 (4 H, m, 2′,5′-H), 2.49 (1 H, m, 1-H), 2.30 (1 H, m, 2-H), 1.95 (4 H, m, 3′,4′-H), 1.27 and 0.55 (each 1 H, m, 1a-H); ^{13}C NMR ($CDCl_3$) δ 180.25 (8-C), 176.63 (5-C), 159.47 (7-C/urethane), 156.62 (urethane/7-C), 144.49 (4a-C), 128.43 (9a/8a-C), 122.91 (8a/9a-C), 109.75 (9-C), 100.16 (6-C), 58.36 (10-C), 51.21 (2′,5′-C), 49.73 (3-C), 29.60 (3′,4′-C), 20.68 (1-C), 16.24 (1a-C), 14.40 (2-C); HRMS found (M^+) 341.1376, $C_{18}H_{19}N_3O_4$ requires (M) 341.1376.

7-(Aziridin-1-yl)-9-[(carbamoyloxy)methyl]-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (22). To a solution of the carbamate 1 (0.014 g, 0.046 mmol) in DMF (1 mL) was added aziridine (0.2 mL), and the resulting solution was stirred at room temperature for 16 h. Water (10 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL) and dried (Na_2SO_4). Chromatography of the residue gave **22** (0.011 g, 76%) as dark red needles: mp 184 °C dec; UV (MeOH) 239 (log ε 4.45), 308 (4.30), 490 nm (3.39); IR ($CHCl_3$) 3532, 3424, 1724, 1662, 1632, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.72 (1 H, s, 6-H), 5.27 (2 H, AB, *J* = 12.5, 10-H), 4.62 (2 H, br s, NH_2), 4.24 (2 H, m, 3-H), 2.53 (1 H, m, 1-H), 2.32 (1 H, m, 2-H), 2.18 (4 H, s, 2′,3′-H), 1.29 (1 H, ddd, *J* = 8.0, 8.0, and 3.2, 1a-H), 0.54 (1 H, m, 1a-H); ^{13}C NMR ($CDCl_3$) δ 179.08 (8-C), 177.48 (5-C), 157.73 (C=O), 156.77 (C=O), 146.16 (4a-C), 127.40 (10-C), 49.90 (3-C), 27.51 (aziridine CH_2), 20.59 (1-C), 16.16 (1a-C), 14.65 (2-C); HRMS found (M^+) 313.1063, $C_{16}H_{15}N_3O_4$ requires (M) 313.1063.

9-[(Carbamoyloxy)methyl]-7-(2-methylaziridin-1-yl)-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (23). A solution of the carbamate 1 (0.010 g, 0.033 mmol) in dry DMF (1.5 mL) was treated with an excess of 2-methylaziridine (0.25 mL initially and 0.25 mL 24 h later), and this mixture was stirred at room temperature under nitrogen for 48 h. Workup as above gave **23** (0.0075 g, 68%) as a red solid: mp 176−178 °C; UV (MeOH) 240 (log ε 4.34), 314 (4.17), 499 nm (3.29); IR ($CHCl_3$) 3544, 3424, 1724, 1662, 1630, 1580, 1496, 1338, 1256 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.70 (1 H, s, 6-H), 5.29 (2 H, m, 10-H), 4.64 (2 H, br s, NH_2), 4.25 (2 H, m, 3-H), 2.52 (1 H, m, 1-H), 2.27 (2 H, m, 2,2′-H), 2.08 (2 H, m, 3′-H), 1.42 (3 H, d, *J* = 5.5, 2′-Me), 1.30 and 0.55 (each 1 H, m, 1a-H); HRMS found (M^+) 327.1219, $C_{17}H_{17}N_3O_4$ requires (M) 327.1219.

9-[(Carbamoyloxy)methyl]-7-(pyrrolidin-1-yl)-1,2-dihydro-1a,1a-dimethyl-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (24). A solution of the carbamate **2** (0.010 g, 0.030 mmol) in DMF (1.5 mL) was treated with pyrrolidine (0.008 mL, 0.091 mmol), and the mixture was stirred at room temperature under nitrogen for 15 h. Workup as above gave **24** (0.008 g, 73%) as a purple solid: mp 202 °C dec; UV (MeOH) 254 (log ε 4.40), 330 (4.06), 549 nm (3.52); IR ($CHCl_3$) 3540, 3424, 1724, 1662, 1602, 1544, 1498, 1266 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.28 (2 H, m, 10-H), 5.17 (1 H, s, 6-H), 4.59 (2 H, br s, NH_2), 4.29 (1 H, dd, *J* = 14.0 and 6.3, 3-H), 4.10 (1 H, m, 3-H), 3.59 (4 H, br s, 2′,5′-H), 2.33 (1 H, dd, *J* = 6.9 and 1.0, 1-H), 2.04 (1 H, m, 2-H), 1.94 (4 H, m, 3′,4′-H), 1.17 and 0.67 (each 3 H, s, Me); HRMS found (M^+) 369.1688, $C_{20}H_{23}N_3O_4$ requires (M) 369.1688.

7-(Aziridin-1-yl)-9-[(carbamoyloxy)methyl]-1,2-dihydro-1a,1a-dimethyl-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (25). A solution of the carbamate **2** (0.010 g, 0.030 mmol) in DMF (1.5 mL) was treated with aziridine (0.004 g, 0.091 mmol), and the mixture was stirred at room temperature under nitrogen for 48 h. Workup as above gave **25** (0.0075 g, 75%) as a red solid: mp 169−171 °C; UV (MeOH, qualitative) 241, 313, 495 nm; IR ($CHCl_3$) 3540, 3430, 1725, 1665, 1630, 1580, 1335, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (1 H, s, 6-H), 5.27 (2 H, m, 10-H), 4.69 (2 H, br s, NH_2), 4.26 (1 H, dd, *J* = 14.0 and 6.3, 3-H), 4.06 (1 H, m, 3-H), 2.37 (1 H, dd, *J* = 6.9 and 1.2, 1-H), 2.19 (4 H, s, 2′,3′-H), 2.09 (1 H, m, 2-H), 1.19 and 0.68 (each 3 H, s, Me); HRMS found (M^+) 341.1376, $C_{18}H_{19}N_3O_4$ requires (M) 341.1376.

7-(Aziridin-1-yl)-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo-[1,2-*a*]indole-5,8-dione (26). Distilled aziridine (1.0 mL) was added to a stirred solution of cyclopropapyrroloindole **4** (0.030 g, 0.131 mmol) in anhydrous DMF (3.0 mL) under nitrogen. After the mixture was stirred at room temperature for 15 h under nitrogen, workup as above gave **26** (0.026 g, 84%) as a red solid: mp 163−165 °C; UV (MeOH) 237 (log ε 4.50), 308 (4.33), 491 nm (3.34); IR ($CHCl_3$) 1670, 1636, 1584, 1497, 1475, 1289, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.29 (1 H, s, 9-H), 5.73 (1 H, s, 6-H), 4.26 (2 H, m, 3-H), 2.34 (2 H, m, 1,2-H), 2.18 (4 H, s, 2′,3′-H), 1.28 and 0.55 (each 1 H, m, 1a-H); ^{13}C NMR ($CDCl_3$) δ 178.77 (8-C), 177.71 (5-C), 157.88 (7-C), 146.39 (4a-C), 128.05 (9a/8a-C), 126.74 (8a/9a-C), 115.92 (6-C), 98.96 (9-C), 49.73 (3-C), 27.60 (2′,3′-C), 20.90 (1-C), 16.24 (1a-C), 15.11 (2-C); HRMS found (M^+) 240.090, $C_{14}H_{12}N_2O_2$ requires (M) 240.090.

7-(2-Methylaziridin-1-yl)-1,2-dihydro-3*H*-1,2-cyclopropapyrrolo[1,2-*a*]indole-5,8-dione (27). Distilled 2-methylaziridine (1 mL) was added to a stirred solution of cyclopropapyrroloindole 4 (0.030 g, 0.131 mmol) in anhydrous DMF (3.5 mL) under nitrogen. After the mixture was stirred at room temperature for 15 h under nitrogen, more 2-methyl-

aziridine (1 mL) was added and the reaction was monitored by TLC. After a further 48 h, workup as above gave **27** (0.026 g, 79%) as a red oil: UV (MeOH) 237 (log ε 4.38), 308 (4.20), 493 nm (3.23); IR ($CHCl_3$) 3013, 1668, 1634, 1581, 1497, 1288, 1259, 1144 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.26 (1 H, s, 9-H), 5.68 (1 H, s, 6-H), 4.25 (2 H, m, 3-H), 2.34 (2 H, m, 1,2-H), 2.24 (1 H, m, 2′-H), 2.07 (2 H, m, 3′-H), 1.41 (3 H, d, J = 5.5, 2′-Me), 1.27 and 0.58 (each 1 H, m, 1a-H); ^{13}C NMR ($CDCl_3$) δ 179.03 (8-C), 177.91 (5-C), 158.04 (7-C), 146.37 (4a-C), 128.08 (9a/8a-C), 127.00 (8a/9a-C), 115.25 (6-C), 98.93 (9-C), 49.82 (3-C), 36.15 (2′-C), 34.53 (3′-C), 21.05 (1-C), 17.64 (2′-Me), 16.35 (1a-C), and 15.22 (2-C); HRMS found (M^+) 254.1059, $C_{15}H_{14}N_2O_2$ requires (M) 254.1055.

7-(Aziridin-1-yl)-9-[(carbamoyloxy)methyl]-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (28). Distilled aziridine (1 mL) was added to a stirred solution of the carbamate **5** (0.030 g, 0.103 mmol) in anhydrous DMF (3.5 mL) under nitrogen. After the mixture was stirred at room temperature for 72 h under nitrogen, workup as above gave **28** (0.021 g, 68%) as a red solid: mp 185 °C dec; UV (MeOH) 233 (log ε 4.24), 308 (4.13), 483 nm (3.18); IR (KBr) 3440, 3332, 1692, 1634, 1579, 1495, 1408, 1353, 1260 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-*d*) δ 5.73 (1 H, s, 6-H), 5.52 (2 H, br s, NH_2), 5.21 (2 H, s, 10-H), 4.20 (2 H, t, J = 7.4, 3-H), 2.93 (2 H, t, J = 7.4, 1-H), 2.53 (2 H, m, 2-H), 2.19 (4 H, s, 2′,3′-H); HRMS found (M^+) 301.1086, $C_{15}H_{15}N_3O_4$ requires (M) 301.1086.

9-[(Carbamoyloxy)methyl]-7-(2-methylaziridin-1-yl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (29). Distilled 2-methylaziridine (1 mL) was added to a stirred solution of the carbamate **5** (0.030 g, 0.103 mmol) in anhydrous DMF (3.5 mL) under nitrogen. After the mixture was stirred at room temperature for 72 h under nitrogen, workup as above gave **29** (0.019 g, 58%) as a red solid: mp 201 °C dec; UV (MeOH) 232 (log ε 4.28), 308 (4.13), 486 nm (3.21); IR (KBr) 3342, 3201, 1725, 1663, 1622, 1576, 1497, 1262, 1077 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-*d*) δ 5.72 (1 H, s, 6-H), 5.24 (2 H, s, 10-H), 4.92 (2 H, br s, NH_2), 4.21 (2 H, t, J = 7.4, 3-H), 2.93 (2 H, t, J = 7.4, 1-H), 2.56 (2 H, pentet, J = 7.4, 2-H), 2.27 (1 H, m, 2′-H), 2.08 (2 H, m, 3′-H), 1.43 (3 H, d, J = 5.5, 2′-Me); ^{13}C NMR ($CDCl_3$–DMSO-*d*) δ 179.43 (8-C), 177.93 (5-C), 157.73 (7-C/urethane), 156.71 (urethane/7-C), 144.01 (4a-C), 126.67 (8a/9a-C), 124.91 (9a/8a-C), 114.98 (6-C), 111.70 (9-C), 57.95 (10-C), 46.77 (3-C), 35.95 (2′-C), 34.34 (3′-C), 27.00 (1-C), 22.94 (2-C), 17.56 (2′-Me); HRMS found (M^+) 315.1227, $C_{16}H_{17}N_3O_4$ requires (M) 315.1219.

7-(Aziridin-1-yl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (30). Distilled aziridine (1 mL) was added to a stirred solution of pyrroloindole **7** (0.030 g, 0.138 mmol) in anhydrous DMF (3.0 mL) under nitrogen. After the mixture was stirred at room temperature under nitrogen for 15 h, workup as above gave **30** (0.023 g, 73%) as a red solid: mp 184–186 °C; UV (MeOH) 231 (log ε 4.34), 308 (4.22), 479 nm (3.19); IR ($CHCl_3$) 1670, 1638, 1583, 1475, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (1 H, s, 9-H), 5.75 (1 H, s, 6-H), 4.22 (2 H, t, J = 7.3, 3-H), 2.85 (2 H, t, J = 7.3, 1-H), 2.56 (2 H, pentet, J = 7.3, 2-H), 2.19 (4 H, s, 2′,3′-H); ^{13}C NMR ($CDCl_3$) δ 179.11 (8-C), 178.06 (5-C), 157.96 (7-C), 144.55 (4a-C), 130.90 (9a/8a-C), 128.82 (8a/9a-C), 116.20 (6-C), 99.84 (9-C), 46.80 (3-C), 27.72 (2′,3′-C), 27.65 (1-C), 23.64 (2-C); HRMS found (M^+) 228.0893, $C_{13}H_{12}N_2O_2$ requires (M) 228.0899.

7-(2-Methylaziridin-1-yl)-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (31). Distilled 2-methylaziridine (1 mL) was added to a stirred solution of pyrroloindole **7** (0.020 g, 0.092 mmol) in anhydrous DMF (3.0 mL) under nitrogen. After the mixture was stirred at room temperature under nitrogen for 15 h, more 2-methylaziridine (1 mL) was added. The reaction was monitored by TLC, and after a further 5 h, workup as above gave **31** (0.018 g, 82%) as a red solid: mp 137–139 °C; UV (MeOH) 231 (log ε 4.37), 308 (4.25), 483 nm (3.24); IR ($CHCl_3$) 1668, 1636, 1581, 1496, 1475, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (1 H, s, 9-H), 5.72 (1 H, s, 6-H), 4.22 (2 H, t, J = 7.3, 3-H), 2.85 (2 H, t, J = 7.3, 1-H), 2.56 (2 H, pentet, J = 7.3, 2-H), 2.26 (1 H, m, 2′-H), 2.08 (2 H, m, 3′-H), 1.42 (3 H, d, J = 5.5, 2′-Me); ^{13}C NMR ($CDCl_3$) δ 179.26 (8-C), 178.15 (5-C), 157.99 (7-C), 144.39 (4a-C), 128.58 (9a/8a-C), 126.09 (8a/9a-C), 115.42 (6-C), 99.69 (9-C), 46.77 (3-C), 36.14 (2′-C), 34.56 (3′-C), 27.65 (1-C), 23.62 (2-C), 17.65 (2′-Me); HRMS found (M^+) 242.1052, $C_{14}H_{14}N_2O_2$ requires (M) 242.1055.

3-[(Carbamoyloxy)methyl]-1,2-dimethyl-5-(pyrrolidin-1-yl)indole-4,7-dione (32). To a stirred solution of the carbamate **8** (0.015 g, 0.054 mmol) in DMF (1 mL) was added pyrrolidine (0.04 g, 0.54 mmol), and the mixture was stirred at room temperature overnight. Workup as above gave **32** (0.012 g, 71%) as a purple solid: mp 238 °C dec; UV (MeOH) 225 (log ε 4.22), 250 (4.31), 325 (4.10), 541 nm (3.57); IR ($CHCl_3$) 3024, 2360, 1726, 1662, 1603 cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-*d*) δ 6.00 (2 H, br s, NH_2), 5.14 (2 H, s, CH_2OCONH_2), 5.10 (1 H, s, 6-H), 3.90 (3 H, s, NMe), 3.60 (4 H, m, 2′,5′-H), 2.26 (3 H, s, 2-Me), 1.97 (4 H, m, 3′,4′-H); HRMS found (M^+) 317.1375, $C_{16}H_{19}N_3O_4$ requires (M) 317.1375.

5-(Aziridin-1-yl)-3-[(carbamoyloxy)methyl]-1,2-dimethylindole-4,7-dione (33). To a stirred solution of the carbamate **8** (0.019 g, 0.068 mmol) in DMF (1.5 mL) was added aziridine (0.15 g, 3.4 mmol). The mixture was stirred at room temperature overnight. Workup as above gave **33** (0.016 g, 81%) as a dark orange solid: mp 219 °C dec; UV (MeOH) 233 (log ε 4.38), 308 (4.25), 479 nm (3.36); IR ($CHCl_3$) 3017, 2900, 2366, 1728, 1682, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (1 H, s, 6-H), 6.89 (2 H, s, CH_2OCONH_2), 4.60 (2 H, br s, NH_2), 3.86 (3 H, s, NMe), 2.29 (3 H, s, 2-Me), 2.18 (4 H, s, 2′,3′-H); HRMS found (M^+) 289.1063, $C_{14}H_{15}N_3O_4$ requires (M) 289.1062.

3-[(Carbamoyloxy)methyl]-1,2-dimethyl-5-(2-methylaziridin-1-yl)indole-4,7-dione (34). To a stirred solution of the carbamate **8** (0.016 g, 0.057 mmol) in DMF (2 mL) was added 2-methylaziridine (0.16 g, 2.8 mmol). The mixture was stirred at room temperature overnight. Workup as above gave **34** (0.016 g, 88%) as a red-orange solid: mp 198–199 °C; UV (MeOH) 234 (log ε 4.38), 308 (4.25), 482 nm (3.34); IR ($CHCl_3$) 3017, 2957, 2366, 1728, 1682, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (2 H, br s, NH_2), 5.66 (1 H, s, 6-H), 5.41 (2 H, s, CH_2OCONH_2), 3.87 (3 H, s, NMe), 2.25 (4 H, m, 2-Me, 2′-H), 2.07 (2 H, m, 3′-H), 1.39 (3 H, d, J = 5.4, 2′-Me); ^{13}C NMR ($CDCl_3$) δ 179.08, 178.47, 157.13 ($CONH_2$), 156.77, 137.72, 127.89, 116.18, 115.93, 78.14, 56.26 (CH_2OCONH_2), 35.80 (2′-C), 34.28 (3′-C), 32.13 (NMe), 17.66 (2′-Me), 9.43 (2-Me); HRMS found (M^+) 303.1220, $C_{15}H_{17}N_3O_4$ requires (M) 303.1219.

1,2-Dimethyl-5-(pyrrolidin-1-yl)indole-4,7-dione (35). To a stirred solution of indolequinone **9** (0.01 g, 0.041 mmol) in DMF (1 mL) was added pyrrolidine (0.03 g, 0.41 mmol), and the mixture was stirred at room temperature overnight. Workup as above gave **35** (0.01 g, 84%) as a purple solid: mp 185–186 °C; UV (MeOH) 222 (log ε 3.95), 248 (3.97), 326 (3.74), 541 nm (3.16); IR ($CHCl_3$) 2948, 2924, 1660, 1602, 1544 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.26 (1 H, s, 3-H), 5.17 (1 H, s, 6-H), 3.89 (3 H, s, NMe), 3.61 (4 H, br s, 2′,5′-H), 2.22 (3 H, s, 2-Me), 1.94 (4 H, m, 3′,4′-H); ^{13}C NMR ($CDCl_3$) δ 180.09, 178.11, 148.89, 135.59, 131.00, 123.20, 105.70, 101.61, 51.06 (4 × CH_2), 31.93 (NMe), 11.87 (2-Me); HRMS found (M^+) 244.1212, $C_{14}H_{16}N_2O_2$ requires (M) 244.1212.

5-(Aziridin-1-yl)-1,2-dimethylindole-4,7-dione (36). To a stirred solution of indolequinone **9** (0.014 g, 0.068 mmol) in DMF (1.5 mL) was added aziridine (0.3 g, 6.8 mmol). The mixture was stirred at room temperature overnight. Workup as above gave **36** (0.01 g, 67%) as a dark red solid: mp 150 °C dec; UV (MeOH) 232 (log ε 4.07), 308 (3.94), 483 nm (2.96); IR ($CHCl_3$) 2924, 1664, 1632, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.34 (1 H, s, 3-H), 5.74 (1 H, s, 6-H), 3.86 (3 H, s, NMe), 2.57 (3 H, s, 2′-Me), 2.17 (4 H, s, 2′,3′-H); ^{13}C NMR ($CDCl_3$) δ 178.35, 178.10, 157.13, 137.25, 131.01, 124.79, 117.40, 106.54, 32.18 (NMe), 27.61 (2′,3′-C), 11.94 (2′-Me); HRMS found (M^+) 216.0899, $C_{12}H_{12}N_4O_2$ requires (M) 216.0899.

1,2-Dimethyl-5-(2-methylaziridin-1-yl)indole-4,7-dione (37). To a stirred solution of indolequinone **9** (0.018 g, 0.087 mmol) in DMF (2 mL) was added 2-methylaziridine (0.1 g, 1.75 mmol). The mixture was stirred at room temperature overnight. Workup as above gave **37** (0.014 g, 70%) as a dark red solid: mp 153–154 °C; UV (MeOH) 232 (log ε 4.22), 308 (4.10), 487 nm (3.12); IR ($CHCl_3$) 2924, 1664, 1632, 1586 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.33 (1 H, s, 3-H), 5.71 (1 H, s, 6-H), 3.66 (3 H, s, NMe), 2.33 (4 H, m, 2-Me, 2′-H), 2.07 (2 H, m, 3′-H), 1.41 (3 H, d, J = 5.5, 2′-Me); ^{13}C NMR ($CDCl_3$) δ 179.28, 178.89, 156.93, 137.50, 129.68, 124.79, 116.65, 106.41, 36.01 (2′-C),

34.50 (3′-C), 32.15 (NMe), 17.63 (2′-Me), 11.93 (2-Me); HRMS found (M^+) 230.1055, $C_{13}H_{14}N_2O_2$ requires (M) 230.1055.

Electrochemical Measurements. Sets of cyclic voltammograms at a sequence of scan rates (20–200 mV s^{-1} for nonaqueous studies and 50–500 mV s^{-1} for aqueous studies) were obtained in triplicate using an E.G. & G. Princeton Applied Research Model 273 potentiostat. A three-electrode system was employed with platinum flag (nonaqueous studies) or hanging mercury drop (Metrohm) (aqueous studies) working electrode. The platinum working electrode was pretreated by anodization and then cathodization for 5 min each in sulfuric acid (0.5 M) at 100 mA, washed thoroughly with deionized water, and dried. The reference electrode was a sodium chloride-saturated calomel electrode (ssce) with a platinum-mesh counter electrode. For nonaqueous studies, mitomycin C and analogues were prepared as 1 mM solutions in freshly distilled DMF (10.0 mL) containing dried tetra-*n*-butyl ammonium tetrafluoroborate (0.1 M) as the supporting electrolyte. Ferrocene was used as an internal reference. For aqueous studies, mitomycin C and analogues were prepared as 0.5 mM solutions in a mixture of freshly distilled DMF (1.0 mL) and a phosphate buffer at pH 7.4 (9.0 mL). All measurements were conducted at 22 (±1) °C in solutions freed of oxygen by bubbling with solvent-saturated nitrogen.

Lipophilicity Measurements. log *P* values were determined as the partition coefficient of cyclopropamitosene compound between equal volumes of 0.04 M phosphate buffer, pH 7.4, and *n*-octanol. Samples were prepared by the addition of the cyclopropamitosene and analogues to equal volumes of 0.04 M phosphate buffer, pH 7.4 (5 mL), and *n*-octanol (5 mL). The two phases were shaken for 24 h and then analyzed by UV, recording absorbance at λ_{max}. log *P* values were calculated using the following equation:

$$\log P = \log_{10}([\text{concentration in } n\text{-octanol}]/[\text{concentration in phosphate buffer}]) = \log_{10}([\text{absorbance of } n\text{-octanol}]/[\text{absorbance of phosphate buffer}])$$

Biological Studies. Chinese hamster V79 cells were exposed to the cyclopropamitosenes and related indolequinones for 3 h at 37 °C under aerobic or anaerobic (N_2) conditions. The toxicity of each compound was characterized by the value of IC_{50}, the concentration required to kill 50% of the cells and this was determined by the MTT assay. This method of measuring toxicity is a proliferation assay based on the ability of viable cells to convert a soluble tetrazolium salt, MTT, into purple Formasan crystals. The optical density of the dissolved crystals is proportional to the number of viable cells. The conditions for carrying out the assay have been described.[23,26] In some experiments, cell survival was also measured by a clonogenic assay.[26] The two methods for assessing toxicity gave comparable results.

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